REMARKS

Claims 12 and 14-16 have been canceled without prejudice or disclaimer of subject matter. Thus, claims 11, 13, and 17-25 are currently pending and under consideration. Claims 11, 13, 17, 18, 24, and 25 have been amended to better define the invention. These amended claims find support throughout the disclosure (e.g., page 9, lines 14-23, original claim 16, and page 4, lines 12-18). Consideration of the amendments and the remarks presented herein is respectfully requested.

I. Rejections based on 35 U.S.C. §112, 1st Paragraph

A. Written Description-Based Rejections

Presently pending claims 11, 13, and 20-25 stand rejected under 35 U.S.C. § 112 as allegedly failing to comply with the written description requirement. The Examiner maintains that "the instant specification only describes the full length IL-21R and contemplates an extracellular domain which comprises amino acids 1-235 or 20-235 of SEQ ID NO:4, but fails to describe an extracellular domain which comprises an amino acid sequence that is at least 85% identical to amino acids 20-235 of SEQ ID NO:4 or a soluble fragment that is capable of binding IL-21" (Office Action, dated March 7, 2006, at p. 4). Applicants have amended claims 11, 13, 24, and 25 to recite "a soluble IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4." Thus, all pending claims are directed toward soluble IL-21Rs that display each of the following six characteristics: 1) solubility; 2) capable of antagonizing IL-21R activity; 3) comprising an extracellular domain of an IL-21R; 4) containing an extracellular domain that is

capable of binding IL-21 or a fragment thereof; 5) containing an extracellular domain that is at least 85% identical to amino acids 20 to 235 of human IL-21R (SEQ ID NO:4), or which comprises amino acids 1 to 235 of SEQ ID NO:4 or amino acids 20 to 235 of SEQ ID NO:4 (claim 17); and 6) capable of inhibiting or reducing the differentiation of a T cell or cell population into a Th2 cell or cell population, or increasing IFNγ levels in a T cell or cell population. However, inasmuch as the Examiner may attempt to assert that the disclosure of the specification is insufficient to describe these newly amended claims, for the following reasons, that rejection is respectfully traversed.

1. The Legal Standard for Written Description

The purpose of the §112 written description requirement is to ensure that an applicant possesses the claimed invention at the time of filing (*see Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956 (Fed. Cir. 2002)). For chemical compounds, such as genes or proteins, an applicant must disclose sufficient identifying characteristics, such that so one of skill can "visualize or recognize the identity" of the invention (*Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)). For a generic claim, the specification must describe "species sufficient to constitute the genera" (*Enzo*, 323 F.3d at 967 (Fed. Cir. 2002)).

2. The Application Describes a Genus of Soluble IL-21Rs as Recited in the Pending Claims

Applicants respectfully submit that they have adequately described a soluble IL-21R genus, as recited in the pending claims by: 1) disclosing the sequence of human IL-21R and incorporating the sequence of murine IL-21R by reference; 2) identifying the extracellular

region of human IL-21R (and therefore disclosing physical properties of IL-21Rs); 3) identifying functional characteristics of antagonist IL-21Rs; and, 4) describing potential alterations in the amino acid sequence of IL-21R that will not significantly change the capacity of IL-21R to bind IL-21 ligands. For these reasons, Applicants submit that the application disclosure, coupled with the skill and knowledge in the relevant art at the time of filing, satisfies the written description requirement of § 112.

Applicants disclose the full length sequence of human IL-21 and IL-21R (Specification, pages 16-18), and note the public disclosure of the mouse IL-21R sequence (Specification, page 16, line 21 (citing *Ozaki* et al. (2000) Proc. Natl. Acad. Sci. USA 97:11439-44 (of record))). *Ozaki* et al. is incorporated by reference at page 5, lines 16-17, of the specification. Alignment of the murine and human IL-21R sequences shows that these polypeptides share about 62% identity ("Amino Acid Sequence Comparison of Mouse and Human IL-21R," submitted herewith as part of an Information Disclosure Statement). As the instant claims are directed to soluble IL-21Rs that vary in the extracellular region by *at most* about 15%, and Applicants have described IL-21R sequences that can differ by about 38%, Applicants respectfully submit that they have shown possession of a genus of antagonist soluble IL-21Rs as recited in the instant claims (i.e., a soluble IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4).

The specification states that the IL-21R extracellular domain consists of about amino acids 20-235 (Specification, page 4, lines 13-15). The specification further discusses an IL-21 antagonist as containing "an IL-21 binding domain" (Specification, page 9, lines 19-20).

The claim language of the pending claims indicates that while an IL-21R may vary in sequence up to about 15% from SEQ ID NO:4, the IL-21R is capable of binding an IL-21 ligand. In addition, claims 11, 13, 24, and 25 recite that the soluble IL-21R used to either inhibit differentiation of a Thp cell (claim 11 and 24) or to increase interferon gamma (IFNγ) levels (claim 13 and 25) are antagonists of IL-21R. A variant soluble IL-21R within the scope of the claims will function to produce the stated result, i.e., these soluble IL-21Rs must either inhibit or reduce the differentiation of Thp cells into Th2 cells (claims 11 and 24) or increase IFNγ levels (claims 13 and 25).

The specification discusses IL-21R sequences with varying degrees of identity to the disclosed human IL-21R sequence. Identity is discussed as preferably ranging from about 50-99% (Specification, page 18, lines 19-26). Variants may include, e.g., those having a mutation in the natural sequence that results in higher affinity of the IL-21R for the IL-21 ligand, those having a mutation resulting in increased resistance to proteolysis, those including a signal peptide, and/or those containing a second peptide (such as an Ig fragment) (*see*, e.g., Specification, page 20, lines 5-10 and page 21, lines 4-12). Thus, a soluble IL-21R may vary from the human sequence of human IL-21R, as long as it retains the ability to bind an IL-21 ligand. In light of the disclosure, one skilled in the art could align the human and mouse IL-21R sequences disclosed in the specification to identify regions and residues of IL-21Rs that are conserved or variable, and thus identify those residues amenable to substitution.

The MPEP §2163 states that addressing the written description requirement of 35 U.S.C. § 112 requires the analysis of several factors.

> Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties,

> functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the methods of making the claimed invention. *See Enzo,* 323 F.3d at 964 (Fed. Cir. 2002) (citing *Regents of the University of California*, 119 F.3d at 1566 (Fed. Cir. 1997)).

Applicants submit that the specification conveys that they were in possession of a genus of soluble IL-21Rs as recited in the claims based on disclosing the structure of human and mouse IL-21R sequences, disclosing the function of soluble IL-21Rs (antagonistic; inhibiting or reducing Thp cell differentiation, or increasing IFNγ levels), disclosing biological properties of the IL-21Rs recited in the claims (soluble; ligand-binding capacity), and disclosing methods of making soluble IL-21Rs (indicating types of amino acid changes that may be introduced into the disclosed IL-21R sequences, and disclosing the mouse and human IL-21R sequences for comparison). Thus, Applicants respectfully submit that they have adequately described a genus of soluble IL-21Rs as recited in the claimed methods, and respectfully request reconsideration and withdrawal of the written description-based rejection of pending claims 11, 13, and 20-25.

3. The Knowledge of One Skilled in the Relevant Art Provides Soluble IL-21Rs as Recited in the Pending Claims.

The Examiner states that "[t]he specification does not describe which amino acids of amino acids 20 to 235 of SEQ ID NO:4, can be altered without altering the desired activity of binding to IL-21 receptor. . . and . . . the skilled artisan would not be able to visualize or describe what has not been conceived" (Office Action, dated March 7, 2006 at p. 4). However, Applicants respectfully submit that one of ordinary skill in the art would recognize that Applicants were in possession of a genus of soluble IL-21Rs as recited in the pending claims. As discussed above, an applicant must disclose sufficient identifying characteristics of a chemical

compound such that one of skill in the art can "visualize or recognize the identity" of the invention (*Regents,* 119 F.3d at 1568 (Fed. Cir. 1997)). However, a specification "need not teach, and preferably omits, what is well known in the art" (*Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986)).

The Examiner believes that the level of skill and knowledge in the art is high (Office Action, dated March 7, 2006, at p. 4). At the time of filing, one skilled in the art would recognize, based on the disclosed human and mouse IL-21R sequences, and the knowledge in the art regarding cytokine receptor-ligand interactions, that alignment of the human and mouse IL-21R sequences with other interleukin receptors would indicate regions of the IL-21R responsible for ligand binding. Alignment of a family of common-gamma chain receptors (e.g., IL-21R, and IL-4, IL-7, and IL-9 receptors) derived from different species (e.g., mouse and human) would indicate regions of IL-21R that should not be significantly altered, or regions that should be altered only with similar amino acids, e.g., replacement of an aliphatic amino acid with another aliphatic amino acid (*see*, e.g., *Bazan* (1990) Proc. Natl. Acad. Sci. USA 87:6934-38 (of record); and *Taylor* (1986) J. Theor. Biol. 119:205-18, 215 (submitted herewith as part of an IDS)). One skilled in the art would recognize that, in general, it is possible to replace residues of IL-21R that form protein tertiary structure, provided that the substituting residue performs a similar function. Guidance concerning what amino acid changes are likely to be phenotypically silent (i.e., changes that are unlikely to significantly affect IL-21R ligand-binding function) can be found throughout the literature, e.g., in *Taylor*, *supra*. Further, *Zvelebil* et al. ((1987) J. Mol. Biol. 195:957-61) (submitted herewith as part of an IDS) teaches the use of sequence alignment (e.g., mouse and human IL-21R) to predict protein secondary structure and protein active sites (e.g., the ligand binding pocket of IL-21R).

In addition to the general teachings available in the art regarding amino acid substitutions, numerous references available at the time of filing discuss the N-terminus of hematopoietic receptors (and specific domains and residues within the N-terminus of these receptors) as being important for ligand binding and receptor signaling (*see,* e.g., *Woodcock* et al. (1994) EMBO J. 13:5176-85 (of record); *Mulhern* et al. (2000) J. Mol. Biol. 297:989-1001 (of record); *Schimmenti* et al. (1995) Exp. Hematol. 23:1341-46 (of record); *LaRosa* et al. (1992) J. Biol. Chem. 267:25402-06 (of record); *Imler* et al. (1992) EMBO J. 11:2047-53 (of record); *Bazan, supra*). For example, gapped BLAST analysis indicates that the human IL-21R disclosed in the current application has 28% identity and 46% homology to the human IL-2 receptor (IL-2Rβ), and that the two receptors score 73.9 bits with a highly significant E-value of $3x10^{-11}$ ("Amino Acid Sequence Comparison of Human IL-21R and Human IL-2Rβ" submitted herewith as part of an IDS). In light of such structural similarity, one skilled in the art could identify functional ligand-binding regions by aligning the disclosed human and mouse IL-21R with the IL-2Rβ. For example, relying on the teachings of *Imler* et al., *supra*, one skilled in the art would recognize that residues 138 to 153 of the human IL-21R, which correspond to about residues 152 to 164 of human IL-2β, should not be significantly altered in order for an IL-21R variant to fall within the scope of the claims. Upon reading the teachings of *Bazan* et al., *supra*, one skilled in the art would recognize that residues directly N-terminal to the conserved proline pair, which is located at about amino acid residues 122-123 of human IL-21R, might also be involved in ligand binding. Upon reading the teachings of *Schimmenti* et al., *supra,* one skilled in the art would recognize that the conserved WSXWS motif is also important for ligand binding. Upon reading the teachings of *Ozaki* et al., *supra* (which is incorporated by reference into the instant application), one skilled in the art could align the human and mouse IL-21R sequences to identify

conserved residues likely to be involved in ligand binding. Applicants respectfully submit that one skilled in the art would immediately recognize the amino acid residues that should be retained, and those that could be modified, to create a ligand-binding soluble IL-21R derived from an extracellular domain of an IL-21R. Applicants respectfully submit that one skilled in the art would recognize that Applicants possessed the genus of antagonist soluble IL-21Rs employed in the instant method claims.

For the reasons set forth above, Applicants respectfully submit that they have shown possession of the claimed invention and have therefore satisfied the written description requirement of 35 U.S.C. § 112. Accordingly, Applicants respectfully request reconsideration and withdrawal of the written description-based rejection of pending claims 11, 13, and 20-25.

B. Enablement-Based Rejections

Presently pending claims 11, 13, 17, 18 and 20-25 stand rejected under 35 U.S.C. § 112 as allegedly failing to comply with the enablement requirement. The Examiner maintains that while the instant specification is enabling for a method of inhibiting or reducing the differentiation of a Thp cell into a Th2 cell by contacting the Thp cell with an antibody to IL-21R, and a method for increasing IFNγ levels in a T cell by contacting a Thp cell with an antibody to IL-21R, the specification "does not reasonably provide enablement" for such similar methods that use "a soluble fragment of an IL-21 receptor, wherein said soluble receptor comprises amino acids 20-234 of SEQ ID NO:4, and is capable of binding IL-21" (Office Action, dated March 7, 2006 at p. 5). The Examiner further maintains that "the specification is also non-enabling for the therapeutic administration of an anti-IL-21 antibody, an antigen binding

fragment of an anti-IL-21 antibody or a soluble fragment of an IL-21 receptor" (*id.*). For the following reasons, that rejection is respectfully traversed.

1. Soluble Fragments of an IL-21Receptor

a. The Legal Standard for Enablement

To satisfy § 112, an applicant must disclose an amount sufficient to allow one skilled in the art to practice the invention without undue experimentation (*see In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991)). However, that some experimentation (or even extensive experimentation) is required to practice a claimed invention does not necessarily invalidate a claim under § 112 (*see In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) (stating "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.")). Therefore, "[e]nablement is not precluded by the necessity for some experimentation . . . . 'The key word is 'undue,' not 'experimentation.'"" (*In re Wands*, 858 F.2d at 736-7 (quoting, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974))). Accordingly, trial-and-error may be acceptable and will not render a claim invalid if the experimentation is routine or the specification provides a reasonable amount of guidance (*see In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991) ("That some experimentation may be required is not fatal . . . .")).

An applicant may claim an invention generically if it is described sufficiently to meet the requirements of § 112, first paragraph (*Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)). If experimentation is required to make the generic invention, the applicant must "provide a reasonable amount of guidance with respect to the direction in

which the experimentation should proceed" (*In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988)). However, an applicant may omit that which is well known or routine in the art (*see Hybritech, Inc. v. Monoclocal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (stating that "a patent need not teach, and preferably omits, what is well known in the art."); *see In re Wands*, 858 F.2d at 736-7 (Fed. Cir. 1988); MPEP § 2164.05(b)). Therefore, to satisfy the enablement requirement of 35 U.S.C. § 112 for pending claims 11, 13, 17, 18, and 20-23, and omitting what is well known, Applicants must provide reasonable guidance to allow one skilled in the art to inhibit or reduce differentiation of a Thp cell or cell population into a Th2 cell or cell population, or to increase IFNγ levels in a T cell or cell population by using, *inter alia*, a soluble IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4 (or wherein the extracellular domain of the IL-21R comprises amino acids 20-235 of SEQ ID NO:4 or amino acids 1-235 of SEQ ID NO:4 (claim 17)). To satisfy the enablement requirement of 35 U.S.C. § 112 for pending claims 24 and 25, and omitting what is well known, Applicants must provide reasonable guidance to enable one skilled in the art to inhibit or reduce the differentiation of a Thp cell or cell population into a Th2 cell or cell population in a subject in need thereof, or increase IFNγ levels in a T cell or cell population in a subject in need thereof by administering to the subject an IL-21R antagonist selected from the group consisting of an anti-IL-21R antibody, an antigen-binding fragment of an anti-IL-21R antibody and a soluble IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4.

b. Applicants' Disclosure and the Knowledge Available to One of Skill in the Art

Applicants have amended claims 11, 13, 24, and 25 to recite "a soluble IL-21R, wherein the soluble IL-21R comprises an extracellular domain of an IL-21R that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4." Thus, all claims are directed toward IL-21Rs that display each of the following six characteristics: 1) solubility; 2) capable of antagonizing IL-21R activity; 3) comprising an extracellular domain of an IL-21R; 4) containing an extracellular domain that is capable of binding IL-21 or a fragment thereof; 5) containing an extracellular domain that is at least 85% identical to amino acids 20 to 235 of SEQ ID NO:4 (or wherein the extracellular domain of the IL-21R comprises amino acids 20-235 of SEQ ID NO:4 or amino acids 1-235 of SEQ ID NO:4 (claim 17)); and 6) capable of inhibiting or reducing the differentiation of a Thp cell or cell population into a Th2 cell or cell population, or increasing IFNγ levels in a T cell or cell population.

It is the Examiner's opinion that "[w]hile an antibody that binds to IL-21Rs would be expected to antagonize IL-21 activity, the art teaches that soluble receptors do not always antagonize the action of the ligand" (Office Action, dated March 7, 2006, at p. 6). The Examiner concludes that one skilled in the art would not be able to predict whether a soluble IL-21R or the extracellular region of IL-21R would inhibit or reduce differentiation of a Thp cell into a Th2 cell, or would increase IFNγ levels. The Examiner cites *Heany* et al. ((1998) J. Leukocyte Biol. 64:135-146) to support the proposition that soluble receptors may agonize or antagonize ligand activity.

Applicants' claimed methods specifically recite that only IL-21 or IL-21R antagonists are to be employed in the pending method claims (see, e.g., independent claim 11). Thus, although certain soluble IL-21Rs may act as agonists, agonist soluble receptors are not within the scope of the presently claimed methods. The Examiner, however, appears to maintain that upon producing a soluble IL-21R, one skilled in the art would be unable to determine whether that soluble IL-21R was an agonist or antagonist of IL-21 or IL-21R (*see* Office Action, dated March 7, 2006 at p. 6). Applicants respectfully submit that the Examples section of the instant application provides numerous methods that one may use to determine whether a soluble IL-21R acts to inhibit or enhance IL-21 signal. For example, Example 8 teaches that IL-21 inhibits IL-12 activity in T cells (Specification at p. 43-45). Thus, one may use the disclosure of Example 8 to test the ability of a soluble IL-21R to regulate IL-12 signaling and the resultant Stat phosphorylation. Therefore, the instant application provides the "reasonable guidance" required to enable one of skill in the art to make and use an antagonist soluble IL-21R as recited in the claimed methods (*see In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988)). As the production of soluble receptors is commonplace (*see*, e.g., *Heany* et al. at p. 140-141), and Applicants have provided the reasonable guidance required to test the activity of soluble IL-21Rs (e.g., Specification, Example 8 at pages 43-45), Applicants respectfully submit that claims reciting "a soluble IL-21R" are enabled.

In addition to the disclosure provided in the instant application, other common techniques are available to allow one of skill in the art to determine whether a soluble IL-21R acts as an agonist or antagonist. For example, enzyme-linked immunosorbant assay (ELISA) is a common technique whereby one may assess the ability of a ligand (e.g., IL-21) to bind to a plate-

bound receptor (e.g., IL-21R).[1/] Using this art-established technique, one could simply test the ability of a soluble IL-21R to block IL-21 binding to plate-bound IL-21R. Such testing is merely routine trial and error, and does not require undue experimentation (*see In re Wands*, 858 F.2d at 736-7 (quoting, *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A 1974))). For this reason, Applicants respectfully submit that one of skill in the art could readily determine whether a soluble IL-21R acts as an agonist or antagonist, and therefore that pending claims 11, 13, and 17-25 satisfy the enablement requirement of 35 U.S.C. § 112.

Finally, the article cited by the Examiner, i.e., *Heany* et al., states at page 136 that "[m]ost commonly, soluble receptors compete with membrane-bound receptors for ligand in the extracellular milieu (Fig. 1B)." Thus, *Heany* et al. suggests that the art is not unpredictable, as one of skill in the art would predict that a soluble IL-21R is a receptor antagonist (*see id.*). The fact that some soluble IL-21Rs may uncommonly (as suggested by *Heany* et al. at page 136) agonize receptor activity does not render the claims nonenabled (*see* MPEP § 2164.08(b)). The MPEP states that when addressing the enablement of claims that encompass inoperative subject matter,[2/] one must ask "whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E. I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)" (MPEP 2164.08(b)). As

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1/ Applicants state that one may use ELISA to measure IL-21-mediated changes in IFNγ levels at page 8, lines 16-18 of the instant specification. Therefore, the instant specification also provides ELISA as a method of determining whether a particular soluble IL-21R is an agonist or antagonist, although such method would also be well known to one of skill in the art.

2/ However, the claims, by reciting "antagonist," exclude subject matter that would not operate to inhibit or reduce differentiation of a Thp cell into a Th2 cell or increase IFNγ levels in a T cell, e.g., IL-21 or IL-21R agonists.

embodiments that would not operate to inhibit or reduce differentiation of a Thp cell into a Th2 cell or increase IFNγ levels in a T cell (i.e., agonistic IL-21Rs and nonfunctional IL-21Rs) are excluded from the scope of Applicants' instant claims (i.e., the claims recite only antagonists), the art suggests that most soluble receptors are antagonistic (*Heany* et al., *supra*, at page 136), and, using the methods disclosed in the Examples or known in the art, one of skill could readily identify antagonistic soluble IL-21Rs, Applicants respectfully submit that pending claims 11, 13, 17, 18, and 20-25 satisfy the enablement requirement of 35 U.S.C. § 112, and request withdrawal of the enablement-based rejections.

2. Administration of a Therapeutic IL-21 or IL-21R Antagonist to a Subject in Need Thereof

It is the Examiner's opinion that "the instant specification does not disclose the administration of a therapeutic agent to inhibit or reduce the differentiation of a Thp cell into a Th2 [cell] or ... increase[] IFNγ levels in a T cell" (Office Action, dated March 7, 2006, at p. 6). This is due to the Examiner's belief that, because "IL-21 has pleitropic effects on the proliferation, differentiation and effector functions of B, T and natural killer cells," one skilled in the art would not be able to predict "whether antagonizing the action of IL-21 would be beneficial" (*id.* at p. 6-7). For the following reasons, Applicants respectfully disagree with the Examiner's assertions.

a. The Legal Standard for Enablement

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject mater sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the

statements contained therein which must be relied on for enabling support

(*In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)). According to § 2164.02 of the MPEP, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate" (MPEP § 2164.02(c)). When questioning correlation, an Examiner is required to take into consideration "whether one skilled in the art would accept the model as reasonably correlating to the condition" (*id.*) However, "[a] rigorous or an invariable exact correlation is not required" based on the holding of *Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985) (stating that ". . . a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence" and all that the law requires is ". . . reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity . . .").

b. Applicants' Disclosure and the Knowledge Available to One of Skill in the Art

It is important to note that claims 24 and 25 are directed only to modulating the effect of IL-21 and IL-21R on T cells (including Thp cells) or populations of T cells. Thus, while the Examiner is correct that "IL-21 has pleitropic effects on the proliferation, differentiation and effector functions of B, T and natural killer cells" (Office Action, dated March 7, 2006 at p. 6), Applicants are not required to analyze the effect of modulating IL-21 or IL-21R on B cells and natural killer cells because claims 24 and 25 only relate to T cell activity (i.e., treatment of a subject in need of inhibition or reduction of Thp cell differentiation into Th2 cells, or treatment of a subject in need of an increase in the level of IFNγ produced by T cells). Thus, the question for enablement is not "whether the administration of an antagonist of IL-21 would be beneficial

or detrimental to a subject" as the Examiner alleges at page 7 of the instant Office Action, but rather, whether Applicants have shown a "reasonable correlation" between the results in the specification and the use asserted by Applicants (*see Cross v. Iizuka*, 753 F.2d at 1050 (Fed. Cir. 1985)).

The specification describes several Th2 cell-associated disorders that would benefit from using an antagonist of IL-21 or IL-21R to reduce the differentiation of a Thp cell into a Th2 cell, or to increase IFNγ levels. For example, on page 2 of the specification Applicants state that Th2-associated disorders include, e.g., "asthma, allergy, and disorders associated with antibody components (e.g., rheumatoid arthritis, multiple sclerosis and lupus)" (Specification, page 2, at lines 19-21 and page 16, lines 11-12). Applicants also disclose that "the IFNγ produced by Th1 cells amplifies Th1 development and inhibits the expansion of Th2 cells" (*id.* at page 2, lines 3-4). Thus, one may use the methods of claims 24 and 25 during the treatment of Th2 cell-associated disorders and disorders in which one wishes to amplify Th1 cell development, inhibit Th2 cell expansion, or increase IFNγ levels in a T cell population.

While compliance with the enablement requirement must be determined at the time of filing, post-filing facts and evidence may be used to support an assertion of the use of a claimed invention in an application (*In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995)). In light of this standard, Applicants respectfully draw the Examiner's attention to U.S. Published Patent Application No. 2006/0039902, filed August 5, 2005 (hereinafter "the '902 application") (submitted herewith as part of an IDS), an application that is similarly directed to IL-21R. Evidence supporting Applicants' assertions that the instant method claims (i.e., claims 24 and 25) may be used to treat Th2 cell-associated disorders, e.g., asthma, allergy, and rheumatoid arthritis, may be found in Example 7 of the '902 application. Example 7 of the '902 application

describes the reduction of arthritic symptoms in a collagen-induced arthritis (CIA) murine model using a soluble IL-21R protein, i.e, an IL-21RFc fusion protein[3/] (the '902 application, Figure 17). This model, which has led to numerous therapies for rheumatoid arthritis (e.g., HUMIRA™ and ENBREL™), reasonably correlates to treatment of arthritis in a subject. (*see*, e.g., *Myers* et al. (1997) Life Sciences 61:1861-78 (submitted herewith as part of an IDS)). Rheumatoid arthritis is disclosed at pages 2 and 16 of the instant application as a Th2-associated disorder amenable to treatment by antagonizing IL-21 or IL-21R activity using the pending method claims. Thus, Applicants have provided experimental substantiation (i.e., alleviation of the symptoms of arthritis with a soluble of IL-21R) for an asserted use of the instant method claims.

IL-21R antagonists (in the form of a soluble fusion protein containing an extracellular domain of an IL-21R fused to an Fc fragment) have also been used to treat the symptoms of systemic lupus erythematosus (SLE) in an MRL-*Fas*^{lpr} mouse model of lupus (the '902 application, Example 13). The copending '902 application shows that a soluble IL-21R antagonist fusion protein significantly reduces dsDNA antibodies (the '902 application, Figure 29), serum total IgG (the '902 application, Figure 30), and the accumulation of IgG in mouse kidney (the '902 application, Figure 31). The MRL-*Fas*^{lpr} mouse model reasonably correlates to treatment of SLE in a subject (*see*, e.g., *Kinoshita* et al. (2000) J. Immunology 164:6046-56, at column 1, lines 1-12 (submitted herewith as part of an IDS)). Lupus is disclosed

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[3/] The soluble IL-21R fusion protein used in the experiments outlined in the '902 application is an antagonistic soluble IL-21R molecule, as determined by ELISA, which showed that the IL-21R fusion protein inhibited the binding of IL-21 to IL-21R (*see* the '902 application at paragraph [0240]; *see also* U.S. Published Patent Application No. 2003/0108549, filed October 4, 2002, at paragraph [0318] (submitted herewith as part of an IDS)).

at pages 2 and 16 of the instant application as a Th2-associated disorder amenable to treatment by antagonizing IL-21 or IL-21R using the pending method claims.

The '902 application also shows that inhibiting IL-21R activity may be used to treat airway inflammation and airway hyperresponsiveness, such as occurs during allergy and asthma (the '902 application, Example 12). The '902 application establishes that loss of IL-21R signal significantly reduces airway response in ovalbumin (OVA)-challenged IL-21R$^{-/-}$ mice treated with aerosolized methacholine (the '902 application, Figure 24). Moreover, IL-21R$^{-/-}$ mice display a significantly reduced number of immune cells and reduced amounts of various cytokines in their bronchoalveolar lavage fluid (the '902 application, Figures 25-27), as well as reduced serum total IgE (the '902 application, Figure 28). The OVA-sensitization / OVA-challenge model reasonably correlates to treatment of allergy and/or asthma in a subject (*see*, e.g., *Iwata* et al. (2003) J. Immunol. 170:3386-91, Abstract (submitted herewith as part of an IDS)). Allergy and asthma are disclosed at pages 2 and 16 of the instant application as Th2 cell-associated disorders amenable to treatment with an IL-21 or IL-21R antagonist using the pending method claims.

In conclusion, the experimental results from several animal models that reasonably correlate to the treatment of arthritis, lupus, allergy and asthma in a subject support Applicants' assertions of a therapeutic use for methods of inhibiting or reducing the differentiation of a Thp cell into a Th2 cell in a subject, and methods of increasing IFNγ levels in a subject. The experimental substantiation found in the '902 application also shows that the models used by Applicants in the instant application to study the effect of IL-21R antagonism on Thp cell differentiation into Th2 cells and the effect of IL-21R antagonism on IFNγ production

by T cells (and the results obtained therewith) reasonably correlate to the asserted therapeutic uses as required under *Cross v. Iizuku*, 753 F. 2d at 1050 (Fed. Cir. 1985).

For at least the reasons set forth above, Applicants respectfully submit that they have shown one of skill in the art how to use therapeutic claims 24 and 25, and therefore that these claims satisfy the enablement requirement of 35 U.S.C. § 112. Therefore, Applicants respectfully request withdrawal of the enablement-based rejections of claims 24 and 25.

II. Rejections based on 35 U.S.C. §112, 2nd Paragraph

The Examiner has objected to claims 12 and 14 as being of improper dependent form for failing to further limit the subject matter of independent claims 11 and 13 (Office Action, dated March 7, 2006 at p. 8). Applicants have canceled claims 12 and 14, rendering this objection moot.

The Examiner has rejected claim 15, stating that recitation of the phrase "comprises an extracellular region of the IL-21R" in claims 15 implies the existence of more than one extracellular region (Office Action, dated March 7, 2006 at p. 8). While Applicants have canceled claim 15, Applicants have amended claims 11, 13, 17, 24 and 25 to recite "extracellular domain" rather than "extracellular region." Support for this amendment is found, e.g., on page 9, lines 19-20 of the instant specification, which states that an IL-21 antagonist may include "a fragment of an IL-21 receptor polypeptide, e.g., an IL-21 binding *domain* of an IL-21 receptor polypeptide" (emphasis added). As the IL-21-binding domain of IL-21R is part of the IL-21R extracellular domain, and the instant specification states that an IL-21-binding domain may be included in an IL-21 antagonist, the limitation "extracellular domain" is supported by the instant application.

The Examiner has rejected pending claims 17-23 under 35 U.S.C. §112, 2nd paragraph as depending on a rejected base claim. For the reasons set forth herein, Applicants believe that all the Examiner's rejections and objections have been answered and overcome. Accordingly, Applicants respectfully request withdrawal of this 35 U.S.C. §112, 2nd paragraph-based rejection of pending claims 17-23.

The Examiner requires clarification of the phrase "soluble fragment of an IL-21R" as recited in claims 11, 13, 24, and 25 (Office Action, dated March 7, 2006 at p. 8). Specifically, the Examiner contends that "[t]here is only one known IL-21 receptor (i.e. SEQ ID NO:4)," and thus the use of the term "an" before "IL-21R" renders the claims unclear as to "which IL-21 receptor is being referred to" (*id.*). Applicants have amended the claims to recite "a soluble IL-21R" rather than "an IL-21R." However, inasmuch as the Examiner may attempt to assert an indefiniteness-based rejection against the claims as newly amended, for the following reasons, that rejection of claims 11, 13, 24 and 25 is respectfully traversed.

A. The Legal Standard for Indefiniteness

The Federal Circuit states that a claim need only "reasonably apprise those skilled in the art of the utilization and scope of the invention" (*Shatterproof Glass Corp. v. Libbey-Owens Ford, Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985)). The fact that a term used in a claim may be interpreted in the alternative does not necessarily render a claim indefinite within the meaning of 35 U.S.C. §112 (*see id.* (stating that "if the language [of the claim] is as precise as the subject matter permits, the courts can demand no more.")). Rather, the test for indefiniteness is whether one skilled in the art would understand the scope of a claim when the claim is read in light of the

specification (*Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986)).

B. The Specification Reasonably Apprises One of Skill in the Art of the Scope of the Phrase "A Soluble IL-21R"

In listing antagonists of IL-21 or IL-21R, the amended claims recite "a soluble IL-21R . . . ." Thus, to satisfy 35 U.S.C. §112, 2nd paragraph, Applicants must disclose sufficient information so that one of skill in the art would understand the scope of "a soluble IL-21R . . . ." Applicants disclose both mouse and human IL-21R sequences, and state that an IL-21R sequence may vary in its degree of identity to the disclosed human IL-21R sequence, preferably ranging from about 50-99% identity (Specification, page 18, lines 19-26). Applicants state that an IL-21R variant may include, e.g., a variant having a mutation in the natural sequence that results in higher affinity for the IL-21 ligand, a variant having a mutation resulting in increased resistance to proteolysis, a variant containing a signal peptide, and/or a variant containing a second peptide (such as an Ig fragment) (*see*, e.g., Specification, page 20, lines 5-10 and page 21, lines 4-12). Thus, as recited in the claims, "a soluble IL-21R" refers to both wild-type and variant forms of IL-21Rs derived from different species, e.g., mouse and human, as long as that soluble IL-21R contains an extracellular domain that is capable of binding IL-21 or a fragment thereof, and wherein the extracellular domain of the soluble IL-21R is at least 85% identical to amino acids 20-235 of SEQ ID NO:4. Therefore, Applicants respectfully submit that the instant specification "reasonably apprise[s] those skilled in the art of the utilization and scope of the invention" (*Shatterproof Glass Corp. v. Libbey-Owens Ford, Co.*, 758 F.2d 613, 624 (Fed. Cir. 1985)).

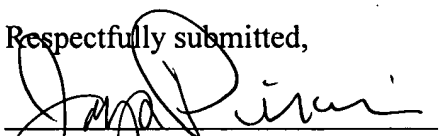
For the above reasons, Applicants respectfully submit that the phrase "a soluble IL-21R" is not indefinite, and therefore that claims 11, 13, 24, and 25 satisfy the requirements of 35 U.S.C. §112, 2nd paragraph. Accordingly, Applicants respectfully request withdrawal of the indefiniteness-based rejection of claims 11, 13, 24, and 25.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. § 112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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